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Follow the Nose

Intranasal delivery may be the key to getting drugs to the brain.

By Trout Lowen

Back in the 1980s, when William H. Frey II, Ph.D., first began investigating the use of natural therapeutic proteins such as insulin and nerve growth factor to treat Alzheimer's disease, his research kept hitting a wall. Frey, a biochemist, neuroscientist, and director of the Alzheimer's Research Center at what was then St. Paul-Ramsey Medical Center (now Regions Hospital), couldn't find a way to get a sufficient quantity of the therapeutic agent past the blood-brain barrier and into the brain.

"We started a clinical trial with a relatively small drug, and it became quite clear that even this molecule wasn't small enough or fat-soluble enough to get into the brain," he recalls. "It was quite frustrating."

Frey's brain must have been working overtime on the problem, however, because he came up with a solution one night while sleeping. In a dream, he was arguing with other scientists over the merits of treating Alzheimer's with growth factors. "I said it would work if we could find a way to get them into the brain. … That was when this idea came to me," he recalls.

The idea was simple: Bypass the blood-brain barrier by going through the nose. Frey already knew that the olfactory and trigeminal nerves provide pathways from the nose to the brain for harmful substances such as heavy metals, viruses, bacteria, and even amoeba, so he wondered if the same pathways couldn't be used to deliver beneficial substances.

He felt so strongly about the idea that he began working on it. In 1989, he filed a patent application for the noninvasive intranasal delivery of targeted therapeutic proteins to the brain to treat neurodegenerative disorders such as Alzheimer's disease. The patent was finally granted in 1997. He later filed for a second patent specifically for intranasal treatment of Alzheimer's. It was granted in 2001.

Frey's patents cover the intranasal administration of a neurologic agent, either alone or in combination with a carrier agent, using a spray, gel, powder, infusion, ointment, injection, or drops to treat Alzheimer's disease, Parkinson's disease, depression, mania, stroke, and aging of the brain.

More than 30 years after Frey had his dream revelation, it's clear he was on to something. During the past five years, researchers working with Frey and independently elsewhere have conducted promising human and animal trials using the intranasal pathways to deliver treatments for Alzheimer's disease, Parkinson's disease, stroke, and other brain disorders. "We're in the early stages but we've seen enough to make people very excited about it," Frey says.

The Pathways

When a drug goes from the nose to the brain, it travels extracellularly along two nerve pathways. One follows the olfactory nerves, which are responsible for smell and are clustered in the upper third of the nasal cavity and connect to the olfactory bulb. The other follows the trigeminal nerves, which are distributed throughout the nasal cavity. Once in the brain, the drug is quickly disbursed into the perivascular spaces. Frey explains that as blood

pumps through the brain, it creates a similar pumping mechanism in those spaces, transporting the drugs throughout the brain.

Frey says selecting which pathway to use for a particular agent is likely important, both in terms of maximizing the drug's efficacy and avoiding side effects. However, researchers still have a lot of work to do to develop methods and devices that can direct substances along one pathway or the other.

Alzheimer's Research

Thus far, the majority of research on intranasal drug delivery has focused on Alzheimer's disease.

Researchers have known for some time that Alzheimer's patients have reduced insulin levels in the brain and reduced glucose uptake in the hippocampal region, which controls memory. Some have suggested that this could contribute to the disease.

But increasing the amount of insulin in the brain was problematic. Administering insulin through the bloodstream puts patients at risk for hypoglycemia, increased insulin resistance, and other related problems. Frey provided another option.

In 2006, he, Suzanne Craft, Ph.D., a professor of psychiatry and behavioral sciences at the University of Washington and director of the Memory Disorders Clinic at the VA Puget Sound Health Center, and her colleagues conducted the first trial of intranasal delivery of insulin looking at the effects on memory. In that trial, patients with Alzheimer's disease and mild cognitive impairment who were given a single dose of intranasal insulin showed measurable improvement in memory within just 20 minutes. "So right away, we realized this was something," Frey says, "because most of the drugs tested for Alzheimer's don't really improve memory. They slow down the cognitive decline of the patient over time compared to placebo, but you're not really seeing significant memory improvement like this."

In 2008, Craft conducted a second trial involving 33 adults with Alzheimer's disease or mild cognitive impairment and 59 adults with normal cognitive function. Each was given five intranasal treatments over six weeks at varying dose levels from placebo to 60 IU. The participants rested for 15 minutes and then were given a battery of cognitive tests involving story recall, verbal learning, and psychomotor skills. The results of that study, published in the *Journal of Alzheimer's Disease* in 2008, showed intranasal treatment had no effect on memory in the adults with normal cognition but improved memory for some of the Alzheimer's and memory-impaired individuals. (Persons with apolipoprotein E-4, a genetic risk factor for late-onset Alzheimer's disease, actually saw a decrease in memory function.) None of the participants showed an increase in blood glucose or insulin levels.

Another study out of the University of Washington reported in *Neurology* in 2008 found that twice-daily intranasal insulin treatment for 21 days improved memory, attention, and functional status in 25 patients with early-stage Alzheimer's disease or mild cognitive impairment.

In September 2011, Craft and colleagues published the results of another trial in which participants were given placebo or insulin through the nose over a period of four months. Those who received the intranasal insulin showed improved memory but also something else. While PET scans of the brain showed a decline in ability to take up glucose over the trial period among both groups, the decline was much more significant in patients who received the placebo. The results, published online in *Archives of Neurology*, indicate that

intranasal insulin may actually do more than just treat the symptoms of Alzheimer's disease.

"It looks like there's a possibility—not proven yet—that if the treatment is started early enough, you might actually be able to delay progression or onset of the disease," Frey says.

That's because when insulin reaches the brain, he explains, it stimulates the formation of insulin-degrading enzyme, which is capable of degrading beta amyloid, one of the principal proteins known to accumulate in the brains of Alzheimer's patients.

Furthermore, insulin seems to reduce the activity of glycogen-synthase kinase-3-beta, the enzyme that phosphorylates tau to create Alzheimer's neurofibrillary tangles. Insulin also helps to maintain or increase synaptic density.

Other Applications

Other researchers are now studying whether Frey's intranasal method might be used to deliver stem cells to patients with Parkinson's disease, and deferoxamine, an iron-binding drug, to those who've had a stroke.

One study, involving Frey and an international research team led by Lusine Danielyan, M.D., of University Hospital of Tübingen and reported in Rejuvenation Research, used intranasal delivery of stem cells to treat Parkinson's disease in rats. Once in the brain, the stem cells were able to detect and migrate to the damaged areas. The result was a dramatic reduction in inflammation and a dramatic increase in mobility and motor function. Frey says the improvement lasted for the duration of the 110-day experiment. Another report out of the Netherlands published in *Pediatric Research* found that the same intranasal stem cell treatment induced functional recovery and a reduction in brain damage in neonatal mice with ischemia.

In a study conducted by Frey and colleagues at the Alzheimer's Research Center and the San Francisco VA Medical Center, which was published in the *Journal of Pharmacology and Experimental Therapeutics* in September 2009, deferoxamine was administered to rats intranasally 48 hours before surgically induced stroke. Compared with the control group, the rats that received the deferoxamine suffered 55 percent less brain damage. Rats given deferoxamine immediately after the surgery also showed similar protective results.

Additional studies exploring the use of intranasal treatments are underway around the world. Approximately 20 papers on intranasal treatment were presented at this year's annual meeting of the Society for Neuroscience. "And it all started in Minnesota," Frey says.